PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P58920L-PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/002849	International filing date *(day/month/year)* 01.07.2004	Priority date *(day/month/year)* 02.07.2003

International Patent Classification (IPC) or national classification and IPC
C07D405/14, C07D409/14, C07D213/74, C07D241/20, C07D401/14, C07D401/12

Applicant
BIOFOCUS DISCOVERY LIMITED et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28.01.2005	02.06.2005

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Telephone No. +49 89 2399-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/002849

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-44	as originally filed

Claims, Numbers

1-20	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1(part), 8 and 9 (part), 10,11,12-19(part),20

because:

☒ the said international application, or the said claims Nos. 18,19 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 10,11,20 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1,8,9,12-19 (each part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☒ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5,6
	No:	Claims	1-4,7-9,12-19
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-9,12-29
Industrial applicability (IA)	Yes:	Claims	1-9,12-17
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

III NON-ESTABLISHMENT

Claims 10, 11 and 20 are completely unclear in scope so that a meaningful examination is not possible (Art. 6 PCT).
Claims 18 and 19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).
Claim 1 has not been searched. The open definitions 'R1 and R2 are joined to form a ring system' or 'R2 is a C1-C6 optionally substituted alkyl' have produced a large number of potentially novelty destroying compounds. This is also true for the eqivalent definitions of R4 and R5 as well as of R6. The search has thus been restricted to the specific groups mentioned for C1-C6alkyl (eg including ethyl, propyl etc.) and to the ring systems (R1 plus R2 or R4 plus R5) which are defined at pages 5/6 bridging paragraph or page 7, respectively of the description.
The definition 'R2 (and also R5) is optionally linked to the scaffold by a linker ...' has also been ignored because its structure is completely unclear.

IV NON-UNITY

The present application relates to Compounds of Formula (I) and (II). The compounds concerned may be used in the treatment of various diseases such as cancer, cardiovascular diseases, AIDS etc. because of the protein kinase activity. The common structural unit refers to a heteroaromatic six-membered ring including nitrogen as ring atom wherein one meta position is substituted by an amino group. This common feature is, however, already known for compounds in the same technical field. The document WO02/094814 describes kinase inhibitors which may be used in the tratment of cancer, vascular diseases, HIV etc. The experimental part includes several compounds which are 3-amino pyridine derivatives. The present application lacks unity because a common special technical feature which may form the contribution over the prior art does not exist. Hence, the present application consists of the following two inventions according to Rule 13(1) and (2) PCT:

(i) Compounds of formula (I) and related claims (1(part),2,3,6-20(part)

(ii)Compounds of formula (II) and related claims (1(part),4,5,6-20(part).

V REASONED STATEMENT

1. PRIOR ART

The documents cited in the International Search Report

D1: WO 01/17995 A (HUNGATE RANDALL W ; BILODEAU MARK T (US); MANLEY PETER J (US); MERCK &) 15 March 2001 (2001-03-15)

D2: WO 02/24681 A (ORTHO MCNEIL PHARM INC) 28 March 2002 (2002-03-28)

D3: JEANJOT P ET AL: "N-(alkyl)-2-amino-1,4-pyrazine derivatives: Synthesis and antioxidative properties of 3- and 3,5-p-hydroxyphenyl-substituted compounds" SYNTHESIS, GEORG THIEME VERLAG. STUTTGART, DE, no. 4, 7 March 2003 (2003-03-07), pages 513-522, XP002287849 ISSN: 0039-7881

D4: WO 01/60816 A (AMGEN INC) 23 August 2001 (2001-08-23)
D1: WO 03/051366 A (ABBOTT LAB) 26 June 2003 (2003-06-26)

D5: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BOWMAN, R. E. ET AL: "Preparation and cyclization of 3-aza-1,5-diketones" XP002308867 retrieved from STN Database accession no. 1973:29148

D6: WO 03/051366 A (ABBOTT LAB) 26 June 2003 (2003-06-26)

have been considered for the examination procedure.

2. NOVELTY

The subject-matter of Claims 1 and 9 is anticipated by D3. (Article 33(2) PCT). D3 discloses several single compounds covered by the definitions of Claims 1 and 9. See the search report for details.

Most of the definitions are generically covered by Claims 1 of D1 or D2. Due to the very specific definitions, the object of present Claim 1 is, however, considered as a novel selection of D1 and D2.

Furthermore, the object of Claims 1-4,7-9 and 12-19 are considered as anticipated by D6. This documents describes Compounds Ib (page 28) which are exemplified by Examples 123 and 130. The mentioned comounds are disclosed as protein kinase inhibitors. The subject-matter of Claims 1 and 4 are also anticipated by D5.

3. INVENTIVE STEP

Pyrazines of Formula (I):

Athough D1 and D2 do not mention the Rho kinase inhibiting activity, these documents concern tyrosine kinase activity with overlapping pharmaceutical profile, i.e. cancer treatment. Due to the very close structural relationship (see novelty, above), D1 and D2 should thus be considered as highly relevant in the assessment of inventive step. The application does not include any information of what has been tested. Page 18 gives only a hint to "activity data" but it is not mentioned which activity is measured. With this information, the problem underlying the present application which may be expected as having been solved, can only be seen in the provision of further pyrazine derivatives. The provision of further novel compounds without indication of a technical effect (activity) is per se not inventive and in particular not inventive, i.e. obvious in view of very close structures as disclosed in D1 and D2. Moreover, Claims 12 and 13 indicate that not all of the compounds would have a therapeutic effect but would probably serve only as a tool for identifying active compounds as it is usual in the field of combinatorial chemistry. In this case, Claim 1 would not be inventive, at all for the mentioned reasons.

Pyridines of Formula (II)

Similar observations as made above for the pyrazines (I) hold equally for the pyridines (II). The closest prior art document is to be seen in D6. It should be noted that this group of compounds may be seen as not unitary in itself because an overlapping compound group is already known with the same activity. With the present information, an inventive, i.e. surprising or unexpected effect of compounds structurally very similar to those of D6 is also not detectable.

4. INDUSTRIAL APPLICABILITY

No objection for Claims 1-17 and 20. For the assessment of the present Claims 18 and 19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VIII CERTAIN OBSERVATIONS (CLAIMS)

1. Claims 7 and 8 refer to parts of the description. This is allowable under Art. 6 PCT only in exceptional cases. It is one of the basic requirements of Art. 6 PCT that a claim should be clear in itself.